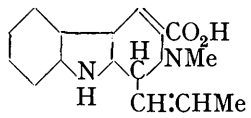
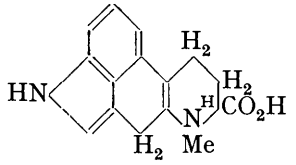
103. *Synthesis of Norharmancarboxylic Acid and its Bearing on the Constitution of Lysergic Acid.*

By HAROLD KING and ERIC T. STILLER.

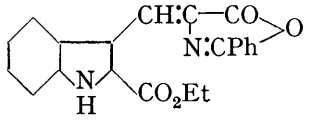
FROM the work of Smith and Timmis in this country and of Jacobs and Craig in the United States it is known that the chief alkaloids of ergot are substituted amides of lysergic acid, $C_{16}H_{16}O_2N_2$. The constitution of lysergic acid is still in doubt. Smith and Timmis (J., 1932, 764) emphasised the similarity between the colour reactions of ergine (lysergic acid amide) and those of indole or its derivatives. On phytochemical grounds, therefore, one might expect, for lysergic acid, a structure derived from tryptophan, and this received expression in the structure (I) put forward by Jacobs and Craig (*J. Biol. Chem.*, 1935, **111**, 455) on experimental grounds. The most recent structure (II) advanced by these

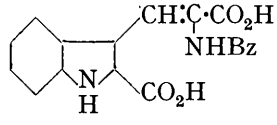
(I.) 

 (II.)

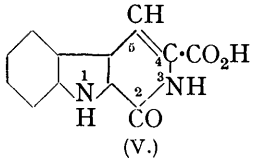
authors (*ibid.*, 1936, **115**, 227), based on further degradative work, can also be derived from tryptophan. These formulæ are partly based on drastic degradation methods applied to an admittedly sensitive molecule, coupled with elegant methods for the isolation of breakdown products, and one may entertain legitimate doubts of formulæ based on such evidence.

In the present communication an account is given of the synthesis of norharmancarboxylic acid, containing the nuclear structure of (I), for comparison with lysergic acid, and of some unusual intermediate products. An approach to this system seemed possible by applying the method developed for the synthesis of *iso*carbostyrils by Bain, Perkin, and Robinson (J., 1914, **105**, 2393) to 2-carbalkoxyindole-3-aldehydes. 2-Carbethoxyindole-3-aldehyde is readily available and on condensation with hippuric acid gave the azlactone, 2-phenyl-4-(2'-carbethoxyindolylidene)oxazolone (III) (Fischer and Pisbor, *Ber.*, 1923, **56**, 2317), a reactive substance which underwent many of the changes shown by Erlenmeyer (*Annalen*, 1893, **275**, 1) to be characteristic of this type of substance. On hydrolysis under the conditions described by Bain, Perkin, and Robinson, this azlactone

(III.) 

 (IV.)

gave 2-*carboxyindole*-3-(α-*benzamido*)*acrylic acid* (IV) as the sole identifiable product. When, however, aqueous potassium hydroxide was replaced by 10% methyl-alcoholic potassium hydroxide, a mixture of products was obtained. During the hydrolysis, the potassium salt of 2-*keto*-2 : 3-*dihydro*-β-*carboline*-4-*carboxylic acid* (V) crystallised. On concentration of the mother-liquors, dilution with water, and neutralisation, a substance, $C_{15}H_{16}O_4N_2$, separated to which, on the basis of the evidence given below, is ascribed the constitution (VI, R = Me), namely, *methyl* 2-*keto*-2 : 3-*dihydro*-β-*carboline*-4-*ortho*-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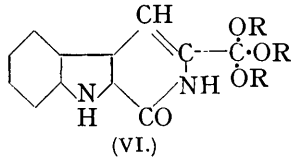
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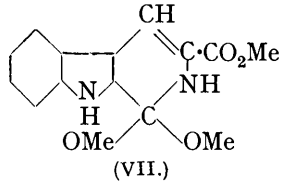
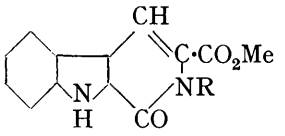

(VII.)

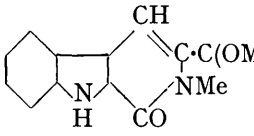
formate. On acidification of the mother-liquors, the acrylic acid (IV), benzoic acid, and a small quantity of (V) were isolated in a pure condition and evidence for the presence

of 2-carboxyindolepyruvic acid (or a derivative) was found by the reaction with ketone reagents.

The orthoformic ester (VI) contains four oxygen atoms, three of which are attached to methyl. During the process of its formation the original ethoxy-group has been eliminated, for the same orthoformic ester was formed if 2-carbomethoxyindole-3-aldehyde was the starting point for the azlactone. In the hydrolytic process which has resulted in the production of the orthoformic ester, the benzoyl and ethyl groups have been eliminated but the oxygen atoms of the carbonyl groups in the original azlactone are retained. The three methoxy-groups must therefore be attached to these carbonyl groups, the only alternative structure being (VII). Of the structures (VI) and (VII), we prefer (VI), since (VII) is, we believe, without analogy among organic compounds. In favour of the structure (VI) may be quoted the observations that the orthoformate gave a purple-brown colour with ferric chloride and formed a potassium salt of phenolic type. On gentle hydrolysis with dilute acids it readily yielded a methyl ester, namely, *methyl* 2-*keto*-2 : 3-*dihydro*-β-*carboline*-4-*carboxylate* (VIII, R = H), a reaction characteristic of orthoformic esters (Skrabal and Ringer, *Monatsh.*, 1921, **42**, 9), and the stability to alkali under conditions

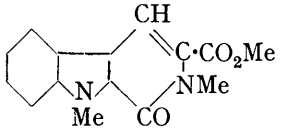
(VIII.)



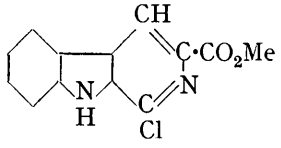


(IX.)

which brought about hydrolysis of the ester (VIII, R = H) speaks against the formula (VII). On methylation of the *potassium* derivative of the orthoformic ester with methyl iodide or of the orthoformic ester with diazomethane, methylation took place on the imide nitrogen atom with formation of *methyl* 2-*keto*-3-*methyl*-2 : 3-*dihydro*-β-*carboline*-4-*orthoformate* (IX). On acid hydrolysis this *N*-methylated orthoformate gave *methyl* 2-*keto*-3-*methyl*-2 : 3-*dihydro*-β-*carboline*-4-*carboxylate* (VIII, R = Me). If methylation of the orthoformate was carried out in acetone solution with methyl sulphate and potassium carbonate, *methyl* 2-*keto*-1 : 3-*dimethyl*-2 : 3-*dihydro*-β-*carboline*-4-*carboxylate* (X) was formed.



(X.)



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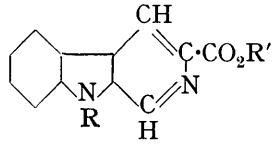


(XII.)

By use of 10% ethyl-alcoholic potassium hydroxide for saponifying the original azlactone (III), the methyl orthoformate (VI, R = Me) was replaced by its *ethyl* homologue (VI, R = Et). The formation of these orthoformic esters and their transformations are not confined to substances derived from the indole nucleus, but are exactly paralleled by the reactions of the azlactone derived from methyl phthalaldehydate (see Stiller, following paper).

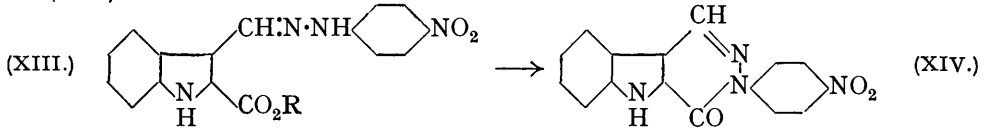
When the carboxycarbolone (V) was treated with 2 molecular proportions of phosphorus pentachloride in phosphorus oxychloride, and the crude products of the reaction separated by conversion into the methyl esters and fractionally crystallised, *methyl* 2-*chloro*-β-*carboline*-4-*carboxylate* (XI) was isolated as the main product. From the acidic mother-liquors a small quantity of the *dihydrochloride* of a *base*, $C_{25}H_{20}O_4N_4$, was obtained. This yielded on treatment with alcohol a colourless amorphous base which was almost insoluble in the usual solvents but could be crystallised from pyridine. On the available evidence we are unable to suggest a satisfactory structure for this substance, but as it contains two methoxy-groups and is dibasic, it must be formed by fusion of two molecules of the original carboxycarbolone with simultaneous reduction of the imide links (to account for the basic character) and loss of one carbon atom.

The chloro-carboline ester (XI) on alkaline hydrolysis gave 2-*chloro*-β-*carboline*-4-*carboxylic acid*. The halogen atom in these substances was firmly bound and could not

be removed catalytically, but on boiling the ester with hydriodic acid and red phosphorus a non-separable mixture was obtained containing the corresponding iodo-acid and its reduction product. When, however, the ester was reduced at 180° with hydriodic acid and red phosphorus, *norharmancarboxylic acid* (XII, R = R′ = H) was readily obtained. This acid, unlike the parent chloro-acid, showed a pronounced blue fluorescence in dilute acid solution and on decarboxylation gave norharman, characterised both as the base and as its picrate. The properties agreed with those recorded for norharman and its picrate by Kermack, Perkin, and Robinson (J., 1921, **119**, 1621). The methyl ester (XII, R = H, R′ = Me) was regenerated from norharmancarboxylic acid by boiling with methyl alcohol and sulphuric acid, but if diazomethane was used, methylation also took place on the indole nitrogen atom with formation of *methyl 1-methyl-β-carboline-4-carboxylate* (XII, R = R′ = Me).

Norharmancarboxylic acid, which may be looked upon as the parent substance of the structure (I) first proposed for lysergic acid, did not react significantly with indole reagents such as *p*-dimethylaminobenzaldehyde and glyoxylic acid, nor did its derivatives. A close comparison was consequently made of the colour reactions of ergometrine (α-alanolamide of lysergic acid) with these reagents and those of indole, 2-methylindole, tryptophan, and the four isomeric α- and β-methylbenzindoles prepared from α- and β-naphthylamines. The greatest similarity was found between the colour reactions of tryptophan and ergometrine, the latter being, however, much more reactive with the glyoxylic acid reagent. Next in order of resemblance came the indoles derived from β-naphthylamine. There can therefore be little doubt that lysergic acid does not contain a β-carboline skeleton, but must contain a more open indole-type of structure (compare Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 767). The formation of a red picrate by ergometrine (Dudley, *Proc. Roy. Soc.*, 1935, *B*, **118**, 478) points in the same direction, since red picrates are formed from indoles which may be substituted in the α- or β-positions or on the nitrogen atom or even by an αβ-ring system such as carbazole, but not apparently by carbolines or analogous structures.

The starting materials in this investigation, 2-carbethoxy- and 2-carbomethoxy-indole-3-aldehydes, reacted with *p*-nitrophenylhydrazine with production of deeply coloured *p*-nitrophenylhydrazones (XIII), which passed smoothly under the influence of heat into the first representatives of a new ring system, 2-p-*nitrophenylindolo*(2′ : 3′ : 4 : 5)*pyridaz-3-one* (XIV).



Experimental.

2-Carbalkoxyindole-3-aldehydes.—*o*-Nitrophenylpyruvic acid was prepared by the condensation of *o*-nitrotoluene and ethyl oxalate by the method of Reissert (*Ber.*, 1897, **30**, 1036). The reduction and ring closure to indole-2-carboxylic acid was effected by the method of Kermack, Perkin, and Robinson (J., 1921, **119**, 1625), by the action of ferrous sulphate on an ammoniacal solution of the acid. The methyl and the ethyl ester were then obtained in excellent yield by the method used by Fischer and Pisbor (*Ber.*, 1923, **56**, 2317) for the preparation of the ethyl ester.

2-Carbethoxyindole-3-aldehyde was prepared from ethyl indole-2-carboxylate following Boyd and Robson's (*Biochem. J.*, 1935, **29**, 555) use of Adams and Levine's (*J. Amer. Chem. Soc.*, 1923, **45**, 2373) modification of the Gatterman hydrogen cyanide method. *2-Carbomethoxyindole-3-aldehyde* was prepared by the same method, but its isolation was indirect. Methylindole-2-carboxylate in ethereal solution was treated with zinc cyanide and dry hydrogen chloride. The imino-chloride obtained was decomposed by boiling with water, but, unlike the carbethoxyindolealdehyde, the carbomethoxy-derivative could not be satisfactorily freed from unchanged ester by fractional crystallisation. The crude aldehyde (14 g.) was therefore dissolved in ethyl alcohol (7·5 c.c.) and treated on the water-bath with aniline (7·5 g.) for 15 minutes, a further quantity of alcohol (70 c.c.) added, and the solution boiled for 30 minutes.

When the red solution was cooled, *2-carbomethoxyindole-3-aldehyde anil* crystallised as a mass of yellow needles (12·75 g.). Recrystallised from alcohol, the anil had m. p. 163—164° (Found : C, 73·3; H, 4·9. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·1%). The anil (12·5 g.) was decomposed by warming with dilute hydrochloric acid for an hour. The aldehyde (9·0 g.) was collected by filtration and on crystallisation from chloroform separated in colourless rectangular plates, m. p. 209—210° (Found : C, 64·8; H, 4·4. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5%).

2-Phenyl-4-(2′-carbethoxyindolylidene)oxazolone (III).—2-Carbethoxyindole-3-aldehyde (28 g.) was intimately mixed with finely powdered hippuric acid (35·2 g.) and anhydrous sodium acetate (12 g.) and suspended in acetic anhydride (160 c.c.). The mixture was heated on a boiling water-bath for 30 minutes; the solids gradually passed into solution and finally the liquid set to a mass of orange needles. When cold, the product was diluted with water, and the solids were collected and ground under sodium bicarbonate solution. The dried solid was further purified by refluxing twice with chloroform (800 c.c.), which removed unchanged aldehyde and other impurities. The azlactone (21 g.) was finally obtained as long, fine, matted, orange needles, m. p. 249—250° (Fischer and Pisbor, *loc. cit.*, give 242° with decomposition) (Found : C, 70·2; H, 4·6; N, 8·0. Calc. : C, 70·0; H, 4·4; N, 7·8%). The chloroform mother-liquors were evaporated to dryness, and the powdered residue re-treated with hippuric acid as described above, a further 15 g. of the azlactone thus being obtained.

2-Phenyl-4-(2′-carbomethoxyindolylidene)oxazolone.—This *azlactone* was prepared by the method described above for the ethyl homologue. The yield was similar and the product after crystallisation from glacial acetic acid had m. p. 253—254° (Found : C, 69·4; H, 4·0. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·1%).

Aqueous Alkaline Hydrolysis of 2-Phenyl-4-(2′-carbethoxyindolylidene)oxazolone.—The azlactone (2 g.) was heated on the water-bath with 8% potassium hydroxide solution (27 c.c.). After 30 minutes a clear, deep red solution was obtained, which on acidification gave a yellowish-white precipitate. On crystallisation from absolute ethyl alcohol *2-carboxyindole-3-(α-benzamido)acrylic acid* (IV) separated in pale yellow, rectangular plates (1·7 g., m. p. 223—224° decomp.) containing one molecule of alcohol of crystallisation (Found for air-dried material : loss at 110°, 11·5; OEt, 10·6; equiv. by titration, 388. $C_{19}H_{14}O_5N_2,C_2H_5{\cdot}OH$ requires loss, 11·6; OEt, 11·4%; equiv. 396. Found for dried material : C, 65·0; H, 4·0; N, 7·9; equiv., 356. $C_{19}H_{14}O_5N_2$ requires C, 65·1; H, 4·0; N, 8·0%; equiv., 350). This acid is very sparingly soluble in boiling water but moderately so in boiling glacial acetic acid and crystallises from the latter solvent in canary-yellow tablets, m. p. 233—234°, containing acetic acid of crystallisation which is tenaciously held.

Ethyl 2-Carbethoxyindole-3-(α-benzamido)acrylate.—The carbethoxy-azlactone (1·5 g.) was boiled under reflux with absolute ethyl alcohol (35 c.c.), and small amounts of anhydrous sodium carbonate added until complete solution had been effected; the colour changed from orange to pale yellow (5 minutes). The hot solution was filtered, and water added to the filtrate to incipient turbidity. On cooling, the *ethyl* ester separated in clusters of pale lemon-yellow, woolly needles (1·4 g.), m. p. 198—199° (Found : C, 68·1; H, 5·5; N, 7·2. $C_{23}H_{22}O_5N_2$ requires C, 68·0; H, 5·5; N, 6·9). The corresponding *methyl* ester was obtained by treating either the methyl or the ethyl ester of the azlactone by the method just described, methyl alcohol being used as the solvent; it crystallised from ethyl alcohol in clusters of yellow plates, m. p. 230—231° (decomp.) (Found : C, 66·6; H, 4·6. $C_{21}H_{18}O_5N_2$ requires C, 66·6; H, 4·8%).

2-Carbethoxyindole-3-(α-benzamido)acrylamide.—The ethyl ester of the azlactone (0·5 g.) was refluxed with ethyl alcohol (8 c.c.) containing concentrated aqueous ammonia (3 c.c.). After 40 minutes the solution was cooled, and the crystalline *amide* (0·4 g.) collected; it crystallised from ethyl alcohol, in which it was sparingly soluble, in fine colourless needles, m. p. 246—247°, resolidifying to a scarlet solid at 249° (Found : C, 66·6; H, 5·0; N, 11·1. $C_{21}H_{19}O_4N_3$ requires C, 66·8; H, 5·1; N, 11·1%). The amide dissolves in hot 2*N*-sodium hydroxide to give a deep orange-red solution, which yields an orange-yellow crystalline precipitate on passage of carbon dioxide. This solid was the *trihydrated sodium* salt of *5-keto-2-phenyl-4-(2′-carboxyindolylidene)-4 : 5-dihydroglyoxaline* (Found : C, 56·3; H, 4·6; N, 10·7; Na, 4·8. $C_{19}H_{12}O_3N_3Na,3H_2O$ requires C, 56·0; H, 4·5; N, 10·3; Na, 5·6%). When an aqueous solution of this salt was acidified with mineral acid, the free *dihydroglyoxalone* separated as an amorphous scarlet precipitate, insoluble in organic solvents (Found : loss at 100°, 2·3; C, 66·3; H, 4·1. $C_{19}H_{13}O_3N_3,\frac{1}{2}H_2O$ requires H_2O, 2·6; C, 67·0; H, 4·1%).

Action of Methyl-alcoholic Potassium Hydroxide on 2-Phenyl-4-(2′-carbethoxyindolylidene)-oxazolone.—The deep red solution formed by dissolving the azlactone (50 g.) in methyl alcohol (1000 c.c.) containing dissolved potassium hydroxide (100 g.) was gently boiled for 3·5 hours,

the crystalline potassium salt of 2-*keto*-2 : 3-*dihydro*-β-*carboline*-4-*carboxylic acid* (V) appearing as fine needles on the walls of the flask within 30 minutes. The potassium salt was collected, dried, and ground with dilute hydrochloric acid. The carbolone acid was washed, dried (yield, 7·7 g.), redissolved in boiling 2*N*-potassium hydroxide and precipitated with dilute hydrochloric acid as a gelatinous mass, which passed into a pale brown, amorphous powder on keeping in contact with the solution. It crystallised from boiling ethyl alcohol, in which it was very sparingly soluble, in thin, colourless, rectangular plates, m. p. 365° (decomp.) after darkening at 340° (Found : C, 62·9; H, 3·4; N, 12·3. $C_{12}H_8O_3N_2$ requires C, 63·1; H, 3·5; N, 12·3%), insoluble in all the common organic solvents except ethyl alcohol or glacial acetic acid and giving a brownish-purple colour with alcoholic ferric chloride. The acid has no basic properties; it is not soluble in sodium hydrogen carbonate solution but loses its crystalline form, especially on warming, with formation of a sodium salt. The *methyl* ester was formed by refluxing the acid (1 g.) with methyl alcohol (16 c.c.) containing sulphuric acid (4 c.c.) and gradually separated in colourless needles (1·0 g.), m. p. 272—273°, soluble in 200 parts of boiling methyl alcohol (Found : C, 64·5; H, 4·3; N, 11·7. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·1; N, 11·6%). On hydrolysis with methyl-alcoholic potassium hydroxide the original acid was recovered, first as the sparingly soluble potassium salt and then as the acid, which was characterised as the ethyl ester. The *ethyl* ester, prepared in the same way, separated from ethyl alcohol in thin colourless diamond-shaped plates, m. p. 260—261° (Found : C, 65·3; H, 4·9. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7%).

The methyl-alcoholic filtrate after removal of the potassium salt was concentrated under reduced pressure to one-half its original volume, diluted with 2 volumes of water, and alkalinity to litmus exactly removed by addition of dilute hydrochloric acid, any local acidity being avoided by vigorous stirring. The crystalline precipitate (20·9 g.) of *methyl* 2-*keto*-2 : 3-*dihydro*-β-*carboline*-4-*orthoformate* (VI, R = Me), after several crystallisations from ethyl alcohol, had m. p. 233—234° (decomp.). It crystallised from alcohol as a mixture of clusters of colourless needles and bold prisms, but if the solution was allowed to cool very slowly, well-formed bold prisms containing one molecule of ethyl alcohol of crystallisation separated. The needle form had m. p. 232—233° and did not depress the m. p. of the prisms; on standing in contact with alcohol, it slowly changed into bold prisms (Found for fresh air-dried material : C, 61·1; H, 6·5; loss at 110°, 13·8; *O*-alkyl, calc. as OMe, 36·0. $C_{15}H_{16}O_4N_2,C_2H_5{\cdot}OH$ requires C, 61·1; H, 6·6; $C_2H_5{\cdot}OH$, 13·8; 3OMe, 1OEt, calc. as 4OMe, 37·1%. Found for material dried at 110° : C, 62·5; H, 5·4; N, 9·7; OMe, 31·8. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·5; N, 9·7; 3OMe, 32·3%). In both Zeisel determinations the demethylated product was identified as the carboxycarbolone, m. p. 365°, and by conversion into the methyl ester, m. p. 272—273°. The orthoformic ester gives a deep purple colour with alcoholic ferric chloride, and a diffused pink band on long standing with an alcoholic solution of *p*-dimethylaminobenzaldehyde in contact with sulphuric acid. Cold dilute hydrochloric acid has no visible effect on the orthoformate, but on warming for a few minutes there is a rapid quantitative conversion of the solid into needles of the methyl ester of the carboxycarbolone, identical in all respects with that described above. The orthoformate is also unaffected by 2*N*-potassium hydroxide at room temperature, but on boiling gives a quantitative yield of the potassium salt of the carboxycarbolone.

The main aqueous alcoholic filtrate from the preparation of the orthoformate was concentrated under reduced pressure, and a further small quantity of orthoformate removed. The aqueous solution was now acidified to Congo-paper, and the orange-yellow crystalline precipitate (17·0 g.) collected. Ethereal extraction of the mother-liquor gave 6·0 g. of solid material, which was added to the precipitate. On exhaustive extraction (Soxhlet) with low-boiling petroleum, benzoic acid (13·3 g.) was removed and the residue, on solution in acetone, left a small quantity of carboxycarbolone (1·1 g.). The acetone liquor on concentration gave 2-carboxyindole-3-(α-benzamido)acrylic acid (IV) (3·2 g.). The residue (4·6 g.) obtained on complete removal of acetone probably contained 2-carboxyindole-3-pyruvic acid, as it readily gave crystalline derivatives with dinitrophenylhydrazine and thiosemicarbazide. The thiosemicarbazone, pale yellow needles, m. p. 267—268°, was the most characteristic derivative, but was not obtained analytically pure.

Action of Methyl-alcoholic Potassium Hydroxide on 2-Phenyl-4-(2′-carbomethoxyindolylidene)oxazolone.—The azlactone (8 g.) was digested with 10% methyl-alcoholic potassium hydroxide as described above for the ethyl ester. 2-Keto-2 : 3-dihydro-β-carboline-4-carboxylic acid (1·1 g.) was obtained through the potassium salt. It had m. p. 365° (decomp.) and was identical in all respects with that previously described. From the mother-liquors, methyl

2-keto-2 : 3-dihydro-β-carboline-4-orthoformate (3·65 g.) was obtained; on crystallisation from ethyl alcohol it had m. p. 234—235° (decomp.), not depressed by the orthoformate obtained from the ethyl ester.

Action of Sodium Methoxide in Methyl Alcohol on 2-Phenyl-4-(2′-carbethoxyindolylidene)-oxazolone.—The azlactone (5·0 g.) in methyl alcohol (100 c.c.) in which sodium (5 g.) had been dissolved was digested on the water-bath for 3 hours. The solid material (5·4 g.) which had separated was collected, ground with dilute hydrochloric acid, washed with water, and extracted with dilute aqueous ammonia. The solid (2·1 g.) undissolved by the ammonia solution was crystallised from ethyl alcohol and proved to be methyl 2-keto-2 : 3-dihydro-β-carboline-4-orthoformate. The ammoniacal liquor on acidification gave 2-keto-2 : 3-dihydro-β-carboline-4-carboxylic acid (0·9 g.), which was obtained crystalline, m. p. 365° (decomp.), by boiling with ethyl alcohol.

Potassium Derivative of Methyl 2-Keto-2 : 3-dihydro-β-carboline-4-orthoformate.—The orthoformate (1 g.), heated in 2*N*-potassium hydroxide (20 c.c.) to 65—70°, dissolved and, on cooling, the *potassium* derivative crystallised in thin, colourless, hexagonal plates, which were collected and dried on porous tile. The salt was partly hydrolysed by water and the potassium could be estimated by titration with *N*/10-hydrochloric acid (Found : K, 9·0, 8·9; loss at 110°, 21·9. $C_{15}H_{15}O_4N_2K,6H_2O$ requires K, 9·0; $5H_2O$, 20·7%. Found for material dried at 110° : K, 11·6, 11·2; MeO, 27·1. $C_{15}H_{15}O_4N_2K,H_2O$ requires K, 11·4; 3MeO, 27·0%). The potassium salt was decomposed by carbon dioxide, and the methyl orthoformate recovered unchanged. The solid recovered from the Zeisel determination was identified as the carboxycarbolone, m. p. 365° (decomp.), and confirmed by conversion into the methyl ester. The insoluble material from the potassium estimations was collected in each case and identified as unchanged orthoformate. The *sodium* derivative, prepared in a similar way, crystallised in thin hexagonal plates (Found : loss at 110°, 26·5. $C_{15}H_{15}O_4N_2Na,6H_2O$ requires H_2O, 25·8%. Found for dried material : Na, 7·0. $C_{15}H_{15}O_4N_2Na$ requires Na, 7·4%).

Methyl 2-Keto-3-methyl-2 : 3-dihydro-β-carboline-4-orthoformate (IX).—(a) The dried potassium derivative of the methyl orthoformate (1·1 g.) was refluxed with excess of methyl iodide for 3 hours. After removal of solvent, the gummy product was treated with water to remove potassium iodide, and the residual syrup dissolved in ethyl alcohol. The *3-methyl orthoformate* (IX) crystallised in stout, colourless, square plates (0·55 g.) and after five crystallisations from alcohol had m. p. 262—263° (with slight darkening and decomp.) (Found : C, 62·9, 63·5; H, 5·8, 6·2, 6·0; N, 9·6; MeO, 30·4, 29·5; MeN, 5·6, 7·0. $C_{16}H_{18}O_4N_2$ requires C, 63·5; H, 6·0; N, 9·3; 3MeO, 30·8; MeN, 9·6%). This product appeared to contain a trace of unmethylated material, as shown by a deepening of colour with a trace of ferric chloride and by the abnormally low m. p. (see below). By gentle warming with dilute hydrochloric acid the methylation product was transformed practically quantitatively into *methyl 2-keto-3-methyl-2 : 3-dihydro-β-carboline-4-carboxylate* (VIII, R = Me), which formed clusters of colourless needles, m. p. 256—258°, from alcohol (Found : C, 65·3, 65·3; H, 4·9, 4·7; MeO, 11·2, 11·5. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; MeO, 12·1%), and did not give a colour with alcoholic ferric chloride.

(b) The methyl orthoformate (0·2 g.) in methyl alcohol (20 c.c.) was treated with diazomethane (5 mols.) in ether (150 c.c.), and the mixture kept for 24 hours. On removal of most of the solvents, the product (IX) (0·18 g.) crystallised in rectangular plates, m. p. 283—284° (Found : C, 63·8; H, 6·3; MeO, 30·6; MeN, 6·1%). It gave no coloration with alcoholic ferric chloride. A mixture of the two products obtained by (a) and (b) melted at 262—264° (with slight darkening and decomp.). When (b) was treated with warm dilute hydrochloric acid, a quantitative conversion into the methyl ester (VIII) was obtained. The product crystallised from ethyl alcohol in clusters of colourless needles, m. p. 258—259°, not depressed by the ester obtained under (a), and gave no coloration with alcoholic ferric chloride.

Methyl 2-Keto-1 : 3-dimethyl-2 : 3-dihydro-β-carboline-4-carboxylate (X).—The parent methyl orthoformate (1·8 g.) was dissolved in boiling dry acetone (125 c.c.), anhydrous potassium carbonate (20 g.) and methyl sulphate (6 c.c.) added, and the mixture refluxed for 3 hours. The filtrate was concentrated (50 c.c.) and, on cooling, the *ester* (X) crystallised in fine colourless needles (1·2 g.). Recrystallisation from ethyl alcohol gave a felt of long, fine, silky needles, m. p. 160—161° (Found : C, 66·5; H, 5·4; MeO, 11·4; MeN, 12·6. $C_{15}H_{14}O_3N_2$ requires C, 66·6; H, 5·2; MeO, 11·5; 2MeN, 21·5%).

Action of Ethyl-alcoholic Potassium Hydroxide on 2-Phenyl-4-(2′-carbethoxyindolylidene)-oxazolone.—The oxazolone (5 g.) was refluxed with ethyl alcohol (100 c.c.) containing potassium hydroxide (10 g.) for 3·5 hours, and the products isolated by methods similar to those already described. The normal carboxycarbolone, m. p. 365°, was identified as its methyl ester. For

the isolation of *ethyl 2-keto-2 : 3-dihydro-β-carboline-4-orthoformate* (VI, R = Et) great care had to be exercised, as traces of acid in excess tended to hydrolyse it to the carbethoxycarbolone. In practice, dilute hydrochloric acid was added to the aqueous alcoholic solution until it was only faintly alkaline; the ethyl orthoformate (1·8 g.) then separated as a crystalline powder. From ethyl alcohol, in which it was readily soluble, it separated in slender colourless prisms, m. p. 192—193° (Found : loss at 100°, 5·3, 5·4. $C_{18}H_{22}O_4N_2,\frac{1}{2}C_2H_5\cdot OH$ requires loss, 6·5%. Found for the dried solid : C, 65·9, 65·1; H, 6·8, 6·8; N, 8·8; EtO, 37·0, 38·6, 37·0. $C_{18}H_{22}O_4N_2$ requires C, 65·7; H, 6·7; N, 8·4; 3EtO, 40·5%). The product recovered from the Zeisel determination had m. p. 365° (decomp.) and was identified through its methyl ester as the carboxycarbolone. The ethyl orthoformate was very much more readily soluble than the corresponding methyl derivative. In alcoholic solution it gave a purple colour with a trace of ferric chloride. It was more readily decomposed than the methyl derivative by dilute acids, 2*N*-hydrochloric acid hydrolysing it at room temperature. Ethyl 2-keto-2 : 3-dihydro-β-carboline-4-carboxylate, thus produced in quantitative yield, crystallised from ethyl alcohol in diamond-shaped plates, m. p. 261—262°, not depressed by the ethyl ester prepared by direct esterification of the acid.

Methyl 2-Chloro-β-carboline-4-carboxylate (XI).—Finely powdered 2-keto-2 : 3-dihydro-β-carboline-4-carboxylic acid (10 g.) was mixed with phosphorus pentachloride (20 g.; 2·2 mols.), and phosphorus oxychloride (30 c.c.) added. The mixture was heated on a vigorously boiling water-bath for 2·5 hours. The solvent was removed by distillation under reduced pressure and then by addition of dry benzene, which was similarly removed. Methyl alcohol (150 c.c.) was added to the residual, partly solid mass, and the mixture refluxed for an hour, the colour changing from purple to dark greenish-brown. The solution was filtered hot from a small quantity of insoluble substance and allowed to crystallise. The cream-coloured needles which separated were fractionally crystallised from ethyl acetate and gave as the major product *methyl 2-chloro-β-carboline-4-carboxylate* in clusters of thin rectangular plates, m. p. 244—245° (Found : C, 59·6; H, 3·5; OMe, 10·4; Cl, 14·2. $C_{13}H_9O_2N_2Cl$ requires C, 59·9; H, 3·5; OMe, 11·9; Cl, 13·6%). On solution in concentrated hydrochloric acid a hydrochloride was formed, m. p. 231—232° (decomp.), crystallising in yellow rectangular plates, decomposed by alcohol with liberation of unchanged ester.

On hydrolysis of the methyl chloro-ester (0·5 g.) with hot 2*N*-sodium hydroxide (15 c.c.) and acidification a partly crystalline precipitate (0·45 g.) was obtained, which on crystallisation from 50% aqueous ethyl alcohol gave *2-chloro-β-carboline-4-carboxylic acid*, m. p. 246—247° (decomp.), as a felt of long fine colourless needles which only showed a trace of fluorescence in solution (Found : loss at 110°, 7·9. $C_{12}H_7O_2N_2Cl,H_2O$ requires H_2O, 6·8%. Found for the dried solid : C, 58·1; H, 3·0; N, 11·0. $C_{12}H_7O_2N_2Cl$ requires C, 58·4; H, 2·9; N, 11·4%). On re-esterification the original methyl ester was obtained.

When the original methyl-alcoholic mother-liquor from which the crude methyl chloro-ester had crystallised was concentrated, a bright yellow, crystalline *dihydrochloride* (3·6 g.) separated, m. p. 213—214° (decomp.) (Found : C, 58·2; H, 4·1; N, 10·4. $C_{25}H_{20}O_4N_4,2HCl$ requires C, 58·5; H, 4·3; N, 10·9%). When treated with methyl or ethyl alcohol, it became white and amorphous, m. p. 303—304° (decomp.). The amorphous base was almost insoluble in the usual solvents and very sparingly soluble in glacial acetic acid, from which it separated in fine colourless needles, m. p. 317—318° (decomp.). The yellow hydrochloride and the amorphous base were soluble in boiling pyridine and the solution when kept slowly deposited the *base* in colourless, well-formed, rectangular tablets, m. p. 333—334° (decomp.) (Found : C, 68·0, 68·0; H, 4·5, 4·4; N, 13·0; MeO, 10·0. $C_{25}H_{20}O_4N_4$ requires C, 68·1; H, 4·6; N, 12·7; 2MeO, 14·1%).

On addition of water to the methyl-alcoholic mother-liquor after removal of the yellow hydrochloride, a further quantity of methyl 2-chloro-β-carboline-4-carboxylate was obtained, the total yield being thus brought up to 45%.

Reduction of Methyl 2-Chloro-β-carboline-4-carboxylate.—The methyl chloro-ester (1·0 g.) was heated with hydriodic acid (6 c.c.; *d* 1·7), red phosphorus (0·4 g.), and potassium iodide (0·4 g.) in a sealed tube at 180° for 6·5 hours. The crystalline solid was collected, dissolved in dilute sodium hydroxide solution, and precipitated with dilute acetic acid. The product, *norharmancarboxylic acid*, pale yellow needles (0·8 g.), was sparingly soluble in glacial acetic acid, from which it separated in lemon-yellow rhomboidal plates, m. p. 309—310° (decomp.) (Found : loss at 110°, 29·9. $C_{12}H_8O_2N_2,1{\cdot}5CH_3\cdot CO_2H$ requires $CH_3\cdot CO_2H$, 29·8%. Found for the dried solid : C, 67·4; H, 3·8; N, 13·3. $C_{12}H_8O_2N_2$ requires C, 67·9; H, 3·8; N, 13·2%). In dilute mineral acids norharmancarboxylic acid exhibited a blue fluorescence. The *methyl*

ester (XII, R = H; R′ = Me) was prepared when the acid (0·2 g.) was refluxed with methyl alcohol (8 c.c.) and sulphuric acid (2 c.c.) for 3·5 hours. The cooled solution was diluted with water and made faintly alkaline with ammonia. The finely divided precipitate crystallised from benzene, in which it was sparingly soluble, in small colourless needles, m. p. 262° (decomp.). When crystallised from alcohol for analysis, it separated in clusters of flattened needles (Found : C, 69·2; H, 4·9; N, 12·0. $C_{13}H_{10}N_2O_2$ requires C, 69·0; H, 4·5; N, 12·4%).

Action of Diazomethane on Norharmancarboxylic Acid.—The acid (0·2 g.), suspended in methyl alcohol (20 c.c.), was treated with an ethereal solution of diazomethane in excess. After 24 hours the solvents were removed, leaving a bright yellow, crystalline material. By trituration with alcohol the yellow material was removed, leaving a colourless crystalline solid (0·1 g.), which on recrystallisation from benzene gave *methyl 1-methyl-β-carboline-4-carboxylate* (XII, R = R′ = Me), m. p. 256—257°, in fine colourless needles (Found : C, 70·2; H, 5·1. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0%). This ester was sparingly soluble in most organic solvents, but dissolved in dilute acids with a yellow colour and bright blue fluorescence.

Decarboxylation of Norharmancarboxylic Acid.—The acid (0·5 g.) was intimately mixed with calcium hydroxide (5 g.) and heated in a distilling flask with a bare flame. The distillate crystallised from benzene in fine colourless needles of norharman (0·34 g.), m. p. 198—199° (Found : C, 78·4; H, 4·8. Calc. : C, 78·5; H, 4·8%). The picrate crystallised from alcohol in bright yellow, feathery needles, m. p. 260—261° (decomp.) (Found : C, 51·3; H, 3·1. Calc. : C, 51·4; H, 2·8%).

2-Carbethoxyindole-3-aldehyde-p-*nitrophenylhydrazone* (XIII, R = Et).—Prepared from the components in boiling ethyl alcohol, this *hydrazone* separated in brownish-red needles. From boiling glacial acetic acid, in which it was sparingly soluble, it crystallised in bronze needles, m. p. 274—275° (decomp.) but solidifying almost immediately to a yellow mass of needles, m. p. *ca.* 335° (Found : C, 60·9; H, 4·4. $C_{18}H_{16}O_4N_4$ requires C, 61·3; H, 4·6%).

When the hydrazone (0·8 g.) was heated at 290—300° under reduced pressure for 1 hour, it gradually lost its deep red colour and changed into yellow needles. The product was boiled with glacial acetic acid to remove unchanged material and the undissolved material (0·6 g.) was crystallised from pyridine, in which it was moderately easily soluble. The product, *2-p-nitrophenylindolo*(2′ : 3′ : 4 : 5)*pyridaz-3-one* (XIV), was thus obtained in pale fawn-coloured needles, m. p. above 365° (Found : C, 62·7; H, 3·3. $C_{16}H_{10}O_3N_4$ requires C, 62·7; H, 3·3%).

2-Carbomethoxyindole-3-aldehyde-p-*nitrophenylhydrazone*, prepared similarly, crystallised from glacial acetic acid in crimson needles, which did not melt but passed on heating into almost colourless needles at 287—292° (Found : C, 60·2; H, 4·2. $C_{17}H_{14}O_4N_4$ requires C, 60·3; H, 4·2%). When heated, this hydrazone gave the same indolopyridazone as was obtained from the ethyl ester.

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